PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
JOHN P. WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	08 MAY 2009
Applicant's or agent's file reference 78185-PCT/JPW/BB	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/08752	17 July 2008 (17.07.2008)	19 July 2007 (19.07.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/395 (2009.01)
USPC - 424/143.1

Applicant PROGENICS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	24 April 2009 (24.04.2009)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 116-124

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 116-124 are so unclear that no meaningful opinion could be formed *(specify)*:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 116-124

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	See Box No. V 2.	YES
	Claims	See Box No. V 2.	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-115 and 125-146	NO
Industrial applicability (IA)	Claims	1-115 and 125-146	YES
	Claims	none	NO

2. Citations and explanations:

Novelty (N) Claims (YES) 8,11,13,16,23, 27, 28, 47, 50,52,55, 61-63,72-73,79,82,84,87,90,102, 103, 125-128,138, 141, 143, 146 YES
Claims (NO) 1-7, 9-10, 12, 14-15, 17-22, 24-26, 29-46, 48,49, 51, 53-54, 56-60, 64-71, 74-78, 80-81, 83, 85, 86, 88, 89, 91-101, 104-115, 129-137, 139-140, 142, and 144-145

Claims 1-7, 9-10, 12, 14-15, 17-22, 24-26, 29-46, 48,49, 51, 53-54, 56-60, 64-71, 74-78, 80-81, 83, 85, 86, 88, 89, 91-101, 104-115, 129-137, 139-140, 142, and 144-145 lack novelty under PCT Article 33(2) as being anticipated by US 2007/0026441 A1 (OLSON et al) (hereinafter 'Olson '441').

Regarding claim 1, Olson '441 teaches a method of inhibiting HIV-1 infection of a susceptible cell by an HIV-1 virus that is, or has become, resistant to (i) one or more HIV protease inhibitors, (ii) one or more HIV reverse transcriptase inhibitors, or (iii) one or more HIV protease inhibitors and one or more HIV reverse transcriptase inhibitors (para [0104]; [0105]), which comprises subjecting the susceptible cell to an effective HIV-1 infection inhibiting dose of (a) a humanized antibody designated PRO 140 wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (Vl) and constant (Cl) regions encoded by the plasmid designated pVK:HuPROl40-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPROl40 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPROl40 (mut B+D+n-VH (ATCC Deposit Designation PTA-4099), wherein the effective HIV-1 infection inhibiting dose comprises from 0.1 mg per kg to 10 mg per kg of the subject's body weight, so as to thereby inhibit the infection of the susceptible cell by HIV-1 that is, or has become, resistant to one or more HIV protease inhibitors, one or more HIV reverse transcriptase inhibitors, or one or more HIV protease inhibitors and one or more HIV reverse transcriptase inhibitors (a form of anti-HIV therapy, para [0104]; such as an HIV protease inhibitor one or more HIV reverse transcriptase inhibitor, para [0105]).

Regarding claim 18, Olson '441 teaches a method of inhibiting HIV-l infection in an HIV-l-infected human subject who is, or has become, resistant to treatment with (i) one or more HIV protease inhibitors, (ii) one or more HIV reverse transcriptase inhibitors, or (iii) one or more HIV protease inhibitors and one or more HIV reverse transcriptase inhibitors (para [0104]; [0105]), which comprises administering to the subject an effective HIV-l infection inhibiting dose of (a) a humanized antibody designated PRO 140 wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (Vl) and constant (Cl) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPR0140 (mut B+D+l)-VH (ATCC Deposit Designation PTA-4099), wherein the effective HIV-1 infection inhibiting dose comprises from 0.1 mg per kg to 10 mg per kg of the subject's body weight, so as to thereby inhibit HIV-1 infection in the subject who is, or has become, resistant to treatment with one or more HIV protease inhibitors, one or more HIV reverse transcriptase inhibitors, or one or more HIV protease inhibitors and one or more HIV reverse transcriptase inhibitors (para [0104]; [0105]).

Regarding claim 68, Olson '441 teaches a method of inhibiting in a human subject the onset or progression of an HIV-1-associated disorder (para [0102]), the inhibition of which is effected by inhibiting fusion of an HIV-1 virus having resistance to (i) one or more HIV protease inhibitors, (ii) one or more HIV reverse transcriptase inhibitors, or (iii) one or more HIV protease inhibitors and one or more HIV reverse transcriptase inhibitors (para [0104]; [0105]), to CCR5+CD4+ target cells in the subject, comprising administering to the subject at a predefined interval effective fusion-inhibitory doses of a humanized antibody designated PRO 140 wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (Vl) and constant (CL) regions encoded by the plasmid designated pVK.:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPROl40 (mut B+D+l)-VH (ATCC Deposit Designation PTA-4099), wherein each administration of the antibody delivers to the subject from 0.1 mg per kg to 10 mg per kg of the subject's body weight, so as to thereby inhibit the onset or progression of the HIV-1-associated disorder in the subject (para [0104]; [0105]).

----------see Supplemental Box----------

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
Claims 84 is objected to because it depends on itself.
Claims 115 is objected to as lacking sufficient antecedent basis the term 'CCRS receptor antagonist' within claim 110, the claim from which it depends.

For the purposes of this search, ISA/US established the following meaning for said claims:

84. The method of claim 83, wherein the one or more nucleoside analogue reverse transcriptase inhibitors (NRTIs) is didanosine (ddI), stavudine (d4T), lamivudine (3TC) or zidovudine
(ZDV).

115. The method of claim 113, wherein the CCRS receptor antagonist is SCH-D, UK-427,857, TAK-779, TAK-652 or GW873140.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V 2.

Regarding claim 69, Olson '441 teaches a method of reducing the likelihood of a human subject's contracting infection by an HIV-1 virus (para [0103]) having resistance to (i) one or more HIV protease inhibitors, (ii) one or more HIV reverse transcriptase inhibitors, or (iii) one or more HIV protease inhibitors and one or more HIV reverse transcriptase inhibitors (para [0104]; [0105]), which comprises administering to the subject at a predefined interval effective fusion inhibitory doses of a humanized antibody designated PRO 140, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VI) and constant (CL) regions encoded by the plasmid designated pVK:HuPROI40-VK (ATCC Deposit Designation PTA4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPROI40 HG2VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPRO140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), wherein each administration of the antibody delivers to the subject from 0.1 mg per kg to 10 mg per kg of the subject's body weight, so as to thereby reduce the likelihood of the subject's contracting an infection by a resistant HIV-1 virus (para [0104]; [0105]).

Regarding claim 89, Olson '441 teaches a method of treating a subject infected with HIV-1 that is, or has become, resistant to (i) one or more HIV protease inhibitors, (ii) one or more HIV reverse transcriptase inhibitors, or (iii) one or more HIV protease inhibitors and one or more HIV reverse transcriptase inhibitors (para [0105]), comprising administering to the subject (a) a monoclonal antibody which (i) binds to a CCR5 receptor on the surface of the subject's CD4+ cells and (ii) inhibits fusion of HIV-I to the subject's CCR5+CD4+ cells (para [0104]).

Regarding claim 131, Olson '441 teaches a method a method of inhibiting HIV-1 infection of a susceptible cell by an HIV-1 virus of subtype A, B, or C (fig 1; para [0038];[0039]), which comprises subjecting the cell to an effective HIV-1 infection inhibiting dose of (a) a humanized antibody designated PRO 140, wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VL) and constant (CL) regions encoded by the plasmid designated pVK:HuPR0140VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPR0140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPR0140 (mut B+D+I)-VH (ATCC Deposit Designation PTA4099), wherein the effective HIV-1 infection inhibiting dose comprises from 0.1 mg per kg to 10 mg per kg of the subject's body weight, so as to thereby inhibit the infection of susceptible cells by HIV-1 of the A, B, or C subtypes (para [0104]).

Regarding claims 2 and 132, Olson '441 teaches the cell susceptible to HIV-1 infection is present in a human subject (para [0091]).

Regarding claims 3, 19, 74 and 133, Olson '441 teaches the anti-CCR5 receptor monoclonal antibody binds to the same CCR5 epitope as that to which PRO 140 binds (para [0104]).

Regarding claims 4, 20, 75, 92-93 and 134, Olson '441 teaches the anti-CCR5 receptor monoclonal antibody is a humanized antibody (para [0104]).

Regarding claims 5, 21, 76, and 135, Olson '441 teaches the monoclonal antibody is the humanized antibody designated PRO 140 (para [0104]).

Regarding claims 6, 22, 77 and 136, Olson '441 teaches the antibody designated PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VI) and constant (CI) regions encoded by the plasmid designated pVK:HuPROI40-VK (ATCC Deposit Designation PTA4097) and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded by the plasmid designated pVg4:HuPROI40 HG2-VH (ATCC Deposit Designation PTA-4098) (para [0104]).

Regarding claims 7, 46, 78 and 137, Olson '441 teaches the HIV-1 virus is, or has become, resistant to (para [0104]) one or more protease inhibitors (PRs) (para [0105]).

Regarding claims 9, 48, 80 and 139, Olson '441 teaches the HIV-1 virus is, or has become, resistant to (para [0104]) one or more reverse transcriptase inhibitors (RTIs) (para [0105]).

Regarding claims 10, 49, 81 and 140, Olson '441 teaches the one or more reverse transcriptase inhibitors (RTIs) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) (para [0105]).

Regarding claims 12, 51, 83 and 142, Olson '441 teaches the one or more reverse transcriptase inhibitors (RTIs) is a nucleoside analogue reverse transcriptase inhibitor (NRTI) (para [0105]).

Regarding claims 14, 53, 85 and 144, Olson '441 teaches the HIV-1 virus is, or has become, resistant both to one or more protease inhibitors (PRs) and to one or more reverse transcriptase inhibitors (RTIs) (para [0105]).

Regarding claims 15, 54, 86 and 145, Olson '441 teaches the one or more reverse transcriptase inhibitors (RTIs) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a nucleoside analogue reverse transcriptase inhibitor (NRTI) (para [0105]).

Regarding claims 17, 56, 88, 129, and 130, Olson '441 teaches the resistant HIV-1 virus is of a subtype selected from subtypes A, B, or C (fig 1; para [0038];[0039]).

Regarding claims 24 and 99, Olson '441 teaches the effective HIV-I infection inhibiting dose is from 0.1 mg per kg to 10 mg per kg of the subject's body weight. (para [0104]).

----------see Supplemental Box----------

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Supplemental Box

Regarding claims 25 and 100, Olson '441 teaches the effective HIV-I infection inhibiting dose is from 0.5 mg per kg to 5 mg per kg of the subject's body weight (para [0130]).

Regarding claims 26 and 101, Olson '441 teaches the effective amount is 5 mg per kg of the subject's body weight (para [0171]; [0104], [0130]).

Regarding claim 29, Olson '441 teaches the effective dose is administered at regular intervals (para [0131]).

Regarding claim 30, Olson '441 teaches the effective HIV-1 infection inhibiting dose is sufficient to achieve in the subject a serum concentration of the antibody of at least 400 ng/ml (para [0097]).

Regarding claim 31, Olson '441 teaches the effective HIV-1 infection inhibiting dose is sufficient to achieve and maintain in the subject a serum concentration of the antibody of at least 1 ug/ml (para [0097]).

Regarding claim 32, Olson '441 teaches the effective HIV-1 infection inhibiting dose is sufficient to achieve and maintain in the subject a serum concentration of the antibody of about 3 to about 12 ug/ml (para [0097]).

Regarding claim 33, Olson '441 teaches the effective HIV-1 infection inhibiting dose is sufficient to achieve and maintain in the subject a serum concentration of the antibody of at least 5 ug/ml (para [0097]).

Regarding claim 34, Olson '441 teaches the effective HIV-1 infection inhibiting dose is sufficient to achieve and maintain in the subject a serum concentration of the antibody of at least 10 ug/ml (para [0097]).

Regarding claim 35, Olson '441 teaches the effective HIV-1 infection inhibiting dose is sufficient to achieve and maintain in the subject a serum concentration oft he antibody of at least 25 ug/ml (para [0097]).

Regarding claim 36, Olson '441 teaches the effective HIV-1 infection inhibiting dose is sufficient to achieve and maintain in the subject a serum concentration of the antibody of at least 50 ug/ml (para [0097]).

Regarding claim 37, Olson '441 teaches the effective HIV infection inhibiting dose is administered at one or more predefined intervals (para [0098]).

Regarding claims 38 and 104, Olson '441 teaches the predefined interval is at least once weekly (para [0098]).

Regarding claims 39 and 105, Olson '441 teaches the predefined interval is every two to four weeks (para [0098]).

Regarding claims 40 and 106, Olson '441 teaches the predefined interval is every two weeks (para [0098]).

Regarding claims 41 and 107, Olson '441 teaches the predefined interval is every three weeks (para [0098]).

Regarding claims 42 and 108, Olson '441 teaches the predefined interval is every four weeks (para [0098]).

Regarding claims 43 and 109, Olson '441 teaches the predefined interval is at least once monthly (para [0098]).

Regarding claim 44, Olson '441 teaches the predefined interval is every six weeks. (para [0098]).

Regarding claim 45, Olson '441 teaches the predefined interval is every eight weeks. (para [0098]).

Regarding claims 57 and 110, Olson '441 teaches the antibody is administered via intravenous infusion (para [0132]).

Regarding claims 58 and 111, Olson '441 teaches the antibody is administered via subcutaneous injection (para [0132]).

Regarding claims 59 and 112, Olson '441 teaches administering to the subject at least one additional antiretroviral agent effective against HIV-1 (para [0137]).

Regarding claim 60, Olson '441 teaches the antiretroviral agent is a CCR5 antagonist (para [0140]) that does not compete with the humanized antibody designated PRO 140 of (a), or the anti-CCRS receptor monoclonal antibody of (b) (Table 2 below para [0030]).

----------see Supplemental Box----------

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Supplemental Box

Regarding claims 64 and 113, Olson '441 teaches the CCR5 antagonist is a non-antibody, small-molecule CCR5 antagonist (para [0140]).

Regarding claim 65, Olson '441 teaches the non-antibody, small-molecule CCRS antagonist is orally administered (para [0106]).

Regarding claim 66, Olson '441 teaches the subject is treatment-naive (para [0100]).

Regarding claim 67, Olson '441 teaches the subject is treatment-experienced (para [0100]).

Regarding claim 70, Olson '441 teaches the subject has been exposed to HIV-1 (para [0103]).

Regarding claim 71, Olson '441 teaches the subject is at risk of being exposed to HIV-I (para [0103]).

Regarding claim 91, Olson '441 teaches the monoclonal antibody is PA14 produced by the hybridoma cell line designated PA14 (ATCC Accession No. HB-1261O), or an antibody that competes with monoclonal antibody PA14's binding to the CCR5 receptor (para [0116]).

Regarding claims 94-96, Olson '441 teaches the monoclonal antibody is the humanized antibody designated PRO 140 , wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VI) and constant (CI) regions encoded by the plasmid designated pYK.:HuPROI40-YK. (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPR0140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099) (para [0104]).

Regarding claim 97, Olson '441 teaches the antibody is administered a plurality of times and the effective amount per administration comprises from 0.01 mg per kg to 50 mg per kg of the subject's body weight (para [0130]).

Regarding claim 98, Olson '441 teaches the antibody is administered a plurality of times and the effective amount per administration comprises from 0.05 mg per kg to 25 mg per kg of the subject's body weight (para [0130]).

Regarding claim 114, Olson '441 teaches the non-antibody CCR5 receptor antagonist is a small organic molecule (para [0117]).

Regarding claim 115, Olson '441 teaches the CCRS receptor antagonist is SCH-D, UK-427,857, TAK-779, TAK-652 or GW873140 (para [0140]).

Claims 23, 27, 28, 102, and 103 lack an inventive step under PCT Article 33(3) as being obvious over Olson '441.

Regarding claim 23, Olson '441 teaches the effective HIV-1 infection inhibiting dose is from 0.05 mg per kg body weight to 25 per kg of the subject's body weight (para [0130]). Olson '441 does not teach the effective HIV-1 infection inhibiting dose is from 0.25 mg per kg to 20 mg per kg of the subject's body weight. It would have been obvious to one of ordinary skill in this art based on routine experimentation to provide the claimed dose because Olson'441 teaches a range that encompasses the claimed range.. One of ordinary skill in this art would have been motivated to do so to optimize he effective HIV-1 infection inhibiting dose.

Regarding claims 27, 28, 102 and 103, Olson '441 teaches the effective amount is from 0.5 mg/kg to 25 mg/kg of the subject's body weight (para [0130]). Olson '441 does not expressly teach that an effective amount comprises 10 mg/kg, 15 mg/kg, or 20 mg/kg, however, such would have been further obvious based on routine experimentation to obtain the invention as claimed because Olson '441 teaches a dose range that encompasses the claimed dose range.

Claims 8, 47, 79 and 138 lack an inventive step under PCT Article 33(3) as being obvious over Olson '441 in view of the article entitled "Amprenavir-resistant HIV-1 exhibits lopinavir cross-resistance and reduced replication capacity" by PRADO et al (hereinafter 'Prado').

Regarding claims 8, 47, 79 and 138, Olson '441 does not teach the one or more protease inhibitors (PRs) is amprenavir (AMP), atazanavir (ATV), indinavir (IDV), lopinavir (LPV), nelfmavir (NFV), ritonavir (RTV) or saquinavir (SQV). Prado teaches an HIV-1 virus that is, or has become, resistant to two protease inhibitors (PRs) wherein the protease inhibitors (PRs) are amprenavir (AMP), and lopinavir (LPV) (Abstract). It would have been obvious to one of ordinary skill in this art to have the invention as claimed in claims 8, 47, 79 and 138 based on the teachings of Prado. One of ordinary skill in this art would have been motivated to do so to treat as many resistant HIV-1 strains as possible.

Claims 11, 13, 50, 52, 82, 84, 141 and 143 lack an inventive step under PCT Article 33(3) as being obvious over Olson '441 in view of the article entitled "Patterns of Resistance Mutations Selected by Treatment of Human Immunodeficiency Virus Type 1 Infection with Zidovudine, Didanosine, and Nevirapine" by HANNA et al (hereinafter 'Hanna').

----------see Supplemental Box----------

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Supplemental Box

Regarding claims 11, 50, 82 and 141, Olson '441 does not teach the one or more non-nucleoside reverse transcriptase inhibitors (NNRTI) is abacavir (ABC), delavirdine (DLV), efavirenz (EFV), nevirapine (NVP) and tenofovir (TFV). Hanna teaches an HIV-1 virus that is, or has become, resistant to a reverse transcriptase inhibitors (RTIs) that is a non-nucleoside reverse transcriptase inhibitor (NNRTI).wherein the non-nucleoside reverse transcriptase inhibitors (NNRTI) is nevirapine (NVP) (Abstract). It would have been obvious to one of ordinary skill in this art to have the invention as claimed in claims 11, 50, 82 and 141 based on the teachings of Hanna. One of ordinary skill in this art would have been motivated to do so to treat as many resistant HIV-1 strains as possible.

Regarding claims 13, 52, 84 and 143, Olson '441 does not teach the one or more nucleoside analogue reverse transcriptase inhibitors (NRTIs) is didanosine (ddI), stavudine (d4T), lamivudine (3TC) and zidovudine (ZDV).Hanna teaches an HIV-1 virus that is, or has become, resistant to a 2 reverse transcriptase inhibitors (RTIs) that is a nucleoside analogue reverse transcriptase inhibitor (NRTI) wherein the 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) is didanosine (ddI) and zidovudine (ZDV) (Abstract). It would have been obvious to one of ordinary skill in this art to have the invention as claimed in claims 13, 52, 84 and 143 based on the teachings of Hanna. One of ordinary skill in this art would have been motivated to do so to treat as many resistant HIV-1 strains as possible.

Claims 61-63 lack an inventive step under PCT Article 33(3) as being obvious over Olson '441 in view of US 2003/0228306 A1 (OLSON et al) (hereinafter 'Olson '306').

Regarding claim 61, Olson '441 teaches administering CCR5 antagonist that does not compete with PRO 140 (synergistic CCR5 antagonist; para [0140]) and further teaches administering multiple antibodies (para [0115]), but does not expressly teach co-administering a non-competitive anti-CCR5 antibody. Olson '306 teaches administering PA14 with a CCR5 antagonist that a monoclonal antibody (para [0214]-[0216], PA12) that does not compete with the antibody designated PRO 140 of (a) (para [0204]-[0206], [0219]-[0220]- note that PRO140 is the humanized version of PA14).O lson '306 also teaches this combination is moderately synergistic (para [0216]). It would have been obvious to one of ordinary skill in this art to provide the method of Olson'441, wherein the non-competitive CCR5 antagonist is an antibody, as taught by Olson'306, to obtain the invention as claimed because Olson'441 teaches administering a synergistic CCR5 antagonist with PRO140 (para [0140]) and teaches administering multiple antibodies (para [0115]) while Olsen'306 teaches an antibody that does not compete with PRO140, as discussed above, and teaches that competing antibodies are not synergistic (para [0216]).

Regarding claim 62, Olson '306 teaches the antibody is a monoclonal antibody (para [0210]).

Regarding claim 63, Olson '306 teaches the antibody may be humanized (para [0104]).

Claims 72-73, 90 and 125-128 lack an inventive step under PCT Article 33(3) as being obvious over Olson '441 in view of the article entitled "Resistance to enfuvirtide, the first HIV fusion inhibitor" by GREENBERG et al (hereinafter 'Greenberg').

Regarding claim 72, Olson '441 teaches a method of inhibiting HIV-1 infection of a susceptible cell by an HIV-1 virus that is, or has become, resistant to a fusion inhibitor (para [0104]; [0105]), which comprises subjecting the susceptible cell to an effective HIV-1 infection inhibiting dose of (a) a humanized antibody designated PRO 140 wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VI) and constant (CI) regions encoded by the plasmid designated pVK:HuPROI40-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPROI40 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPROI40 (mut B+D+n-VH (ATCC Deposit Designation PTA-4099), wherein the effective HIV-1 infection inhibiting dose comprises from 0.1 mg per kg to 10 mg per kg of the subject's body weight, so as to thereby inhibit the infection of the susceptible cell by HIV-1 that is, or has become, resistant to a fusion inhibitor (para [0104]; [0105]). Olson '441 does not teach that the fusion inhibitor is enfuvirtide anti-HIV therapy. Greenberg teaches an HIV virus that has become resistant to the fusion inhibitor enfuvirtide (Abstract). It would have been obvious to one of ordinary skill in this art to provide the method of Olson'441, wherein the fusion inhibitor is enfuvirtide anti-HIV therapy, as taught by Greenberg, to obtain the invention of claim 72 . One of ordinary skill in this art would have been motivated to do so to treat as many resistant HIV-1 strains as possible.

Regarding claim 73, Olson '441 teaches a method of inhibiting HIV-I infection in an HIV-I-infected human subject who is, or has become, resistant to treatment with a fusion inhibitor (para [0104]; [0105]), which comprises administering to the subject an effective HIV-I infection inhibiting dose of (a) a humanized antibody designated PRO 140 wherein PRO 140 comprises (i) two light chains, each light chain comprising the light chain variable (VI) and constant (CI) regions encoded by the plasmid designated pVK:HuPRO140-VK (ATCC Deposit Designation PTA-4097), and (ii) two heavy chains, each heavy chain comprising the heavy chain variable (VH) and constant (CH) regions encoded either by the plasmid designated pVg4:HuPRO140 HG2-VH (ATCC Deposit Designation PTA-4098) or by the plasmid designated pVg4:HuPR0140 (mut B+D+I)-VH (ATCC Deposit Designation PTA-4099), wherein the effective HIV-1 infection inhibiting dose comprises from 0.1 mg per kg to 10 mg per kg of the subject's body weight, so as to thereby inhibit HIV-1 infection in the subject who is, or has become, resistant to treatment with fusion inhibitor (para [0104]; [0105]). Olson '441 does not teach that the fusion inhibitor is enfuvirtide anti-HIV therapy. Greenberg teaches an HIV virus that has become resistant to the fusion inhibitor enfuvirtide (Abstract). It would have been obvious to one of ordinary skill in this art to provide the method of Olson'441, wherein the fusion inhibitor is enfuvirtide anti-HIV therapy, as taught by Greenberg, to obtain the invention of claim 73. One of ordinary skill in this art would have been motivated to do so to treat as many resistant HIV-1 strains as possible.

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

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Regarding claim 90, Olson '441 teaches a method of treating a subject infected with HIV-1 that is, or has become, resistant to fusion inhibitor (para [0104]; [0105]), comprising administering to the subject (a) a monoclonal antibody which (i) binds to a CCR5 receptor on the surface of the subject's CD4+ cells and (ii) inhibits fusion of HIV-I to the subject's CCR5+CD4+ cells (para [0104]; [0105]). Olson '441 does not teach that the fusion inhibitor is enfuvirtide. Greenberg teaches an HIV virus that has become resistant to the fusion inhibitor enfuvirtide (Abstract). It would have been obvious to one of ordinary skill in this art to o provide the method of Olson'441, wherein the fusion inhibitor is enfuvirtide, as taught by Greenberg, to obtain the invention of claim 90 based. One of ordinary skill in this art would have been motivated to do so to treat as many resistant HIV-1 strains as possible.

Regarding claims 125-126, Greenberg teaches resistance to enfuvirtide therapy is associated with one or more mutations in HIV-1 which infects the subject, the mutations selected from G36D, V38A, or N43D and based on the HIV-1 virus (pg 336, Table 1).

Regarding claims 127-128, Olson '441 teaches the resistant HIV-1 virus is of a subtype selected from subtypes A, B, or C (fig 1; para [0038]; [0039]).

Claims 16, 55, 87 and 146 lack an inventive step under PCT Article 33(3) as being obvious over Olson '441 in view of Prado in further view of Hanna.

Regarding claims 16, 55, 87 and 146, Olson '441 does not teach the one or more protease inhibitors (PRs) is amprenavir (AMP), atazanavir (ATV), indinavir (IDV), lopinavir (LPV), nelfmavir (NFV), ritonavir (RTV) and saquinavir (SQV) and the one or more reverse transcriptase inhibitors is selected from the group consisting of abacavir (ABC), delavirdine (DLV), efavirenz (EFV), nevirapine (NVP), tenofovir (TFV), didanosine (ddI), stavudine (d4T), lamivudine (3TC) or zidovudine (ZDV). Prado teaches an HIV-1 virus that is, or has become, resistant to two protease inhibitors (PRs) wherein the protease inhibitors (PRs) are amprenavir (AMP), and lopinavir (LPV) (Abstract). Hanna teaches an HIV-1 virus that is, or has become, resistant to a reverse transcriptase inhibitors (RTIs) that is selected from the group consisting of nevirapine (NVP), didanosine (ddI) and zidovudine (ZDV) (Abstract). It would have been obvious to one of ordinary skill in this art to provide the methods of Olson'441, wherein the protease inhibitor is selected from those taught by Prado and wherein the RTI is selected from those taught by Hanna, to obtain the inventions of claims 16, 55, 87 and 146 . One of ordinary skill in this art would have been motivated to do so to treat as many resistant HIV-1 strains as possible.

Claims 1-115 and 125-146 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.